REMARKS

Favorable reconsideration, reexamination, and allowance of the present patent application are respectfully requested in view of the foregoing amendments and the following remarks. The foregoing amendments have full support in the specification, at least, at paragraphs [0044] (please refer to the published application 2007/0130628), the examples, and in the original claims. No new matter is entered.

Note on Claim Numbering

Please note that in the Preliminary Amendment filed October 15, 2004, a claim was added as "claim 35", which is incorrect since there were 35 claims already present in the application. Therefore, the last claim added in the Preliminary Amendment filed October 15, 2004 should have been "claim 36". The above listing of the claims reflects this change. Also, in the Transmittal Letter filed with the Preliminary Amendment, the 36 claims were indicated for calculating the fees, and so the fees were correctly paid.

Amendments

Claims 1, 3, 10, 19, 20, 21, 23, 28 and 32 are amended. Claims 6, 9-17, 24, 30-33, and 36 are withdrawn as being drawn to a non-elected invention. Claims 10 and 32, while acknowledged as being withdrawn, are also amended for completeness and in the case of a possible rejoinder.

Rejection under 35 U.S.C. § 112, second paragraph

In the Office Action, beginning at page 4, Claims 1-5, 7, 8, 18-23 and 25-29 were rejected under 35 U.S.C. § 112, second paragraph, as reciting subject matters that allegedly are indefinite. Applicant respectfully requests reconsideration of this rejection.

The Office Action states that the term "capable of" allegedly described an intrinisic property of the antibody-secreting cells which does not require the cells to express one of more transgenes, and hence it is allegedly unknown whether this is a limitation. It is noted that these claims further recite the features "and are capable of changing to an immortalized state by means of the transgene or transgenes upon exposure

of the cells to the stimulus." It is clear from these features, in the context of claims 1 and 3, that the stimulus either promotes transgene expression (as set forth in claim 5) or inhibits transgene expression (as set forth in claim 6). In either situation, therefore, the methods of claim 1 and 3 require the cells to express one or more transgenes, either before the stimulus is provided or after the stimulus is provided. Therefore, through further interpretation of the claims, it is clear that the phrase "capable of expressing one or more transgenes" provides a limitation to the claims.

The antecedent basis of claim 21 has been corrected.

For at least the foregoing reasons, Applicant respectfully submits that Claims 1-5, 7, 8, 18-23, 25-29 fully comply with 35 U.S.C. § 112, second paragraph, and therefore respectfully requests withdrawal of the rejection thereof under 35 U.S.C. § 112.

Rejection under 35 U.S.C. § 112, first paragraph

In the Office Action, beginning at page 4, Claims 1-5, 7, 8, 18-23 and 25-29 were rejected under 35 U.S.C. § 112, first paragraph, as reciting subject matters that allegedly fail to comply with the written description requirement. Applicant respectfully requests reconsideration of this rejection.

The Office Action indicates that the claims allegedly contain subject-matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the invention. The Office Action specifically states that it is not clear that applicants were in possession of the starting material used in the claimed process, that is, the genus of p53-/- double deletion mutant animals. The Examiner specifically states that the p53 null ***mouse*** appears to be available, but the genus of p53 null ***animals*** is not "readily available to the public and the specification fails to provide adequate description commensurate with the scope of the claims…."

Although Applicants do not necessarily agree with the Examiner's basis for this rejection, the claims are amended to limit the starting material to a transgenic ***mouse***. As the Examiner has indicated that this embodiment of the invention is fully and adequately described, and no other bases for asserting inadequate written description are provided, the claims are fully and adequately described.

For at least the foregoing reasons, Applicant respectfully submits that Claims 1-5, 7, 8, 18-23 and 25-29 fully comply with 35 U.S.C. § 112, first paragraph, written description, and therefore respectfully requests withdrawal of the rejection thereof under 35 U.S.C. § 112.

In the Office Action, beginning at page 7, Claims 1-5, 7, 8, 18-23 and 25-29 were rejected under 35 U.S.C. § 112, first paragraph, as reciting subject matters that allegedly fail to comply with the enablement requirement. Applicant respectfully requests reconsideration of this rejection.

The Examiner indicates that the specification, while being enabling for providing a p53-/- mouse, does not reasonably provide enablement for providing a genus of p53-/- animal. Although Applicants do not necessarily agree with the Examiner's basis for this aspect of the rejection, the claims are amended to recite a transgenic ***mouse***.

On page 8 of the Office Action, it is questioned whether the means for immortalization are suitable for the purpose of antibody production. Specifically, the Examiner has identified several journal articles that are considered to support this concern. The Examiner states that Yu *et al.* (hereinafter "Yu") teaches that upon expression of the *myc* gene, the p53-/- mouse developed B-cell lymphoma and that *c-myc* is involved in human Burkitt's lymphoma. The Examiner notes that Yu does not disclose the antibody secretion of the lymphoma cells. However, the Examiner states that Benjamin *et al.* (hereinafter "Benjamin") reports an investigation of the cellular origins of undifferentiated lymphomas of the Burkitt's and non-Burkitt's type. The Examiner notes that Benjamin examined immunoglobulin secretion by cell lines and biopsy samples from these tumors and found that Ig secretion by the tumor samples was exclusively IgM.

Furthermore, the Examiner turns to Marinkovic *et al.* (hereinafter "Marinkovic") and indicates that this document reports making B-cell lines which conditionally over-express *myc*, and several weeks into *in vitro* culture, all B-cell lines eventually lost expression of surface IgM. The Examiner further notes that Marinkovic also teaches Myc activation has consistently shown in the art to induce genome instability and rapid accumulation of chromosome abnormalities. As such, the Examiner alleges that it is

unpredictable as to whether conditional overexpressing of *myc* is a good choice for immortalizing B-cells in the context of making antibodies.

First, in response, the study by Benjamin does not provide data which can be extrapolated to the extent that it is possible to conclude that *myc* over-expression will prevent the antibody-secreting cells formed by the method of the present invention from secreting antibodies of the IgG type.

In particular, Benjamin studies cell lines which have been established from biopsy samples taken from patients with undifferentiated Burkitt's and non-Burkitt's lymphomas. As shown in Table 1 of Benjamin, in all but one cell line a translocation involving the *myc* gene is present. However, no further analysis of the genetic mutations underlying the lymphomas is undertaken, and there may be other mutations and cellular malfunctions involved which effect the immunoglobulin type secreted. Moreover, in Benjamin, it is proposed that the lymphoma cells represent an early stage of B cell differentiation, during which antigen-dependent secretion occurs (see final line of abstract). This document provides no disclosure relating to the antibody secretion of mature B cells.

In relation to the disclosure of Marinkovic, it is noted that this document discloses that after several weeks of *in vitro* culture, all B-cell lines eventually lost expression of surface IgM. However, there is no disclosure in this document regarding the levels of secreted antibodies by these cells. Furthermore, it is noted that in Marinkovic, the studies on genomic instability were conducted *in vivo*.

Therefore, it is not possible to extrapolate these findings to the conclusion that *myc* over-expression is not suitable for immortalising antibody secreting cells.

As is indicated by the disclosure of the document by Yokoyama, the person skilled in the art is aware of methods by which the cells of cultured cell lines can best be maintained to ensure their constancy. Therefore, such methods are well within the skill of the art worker, and as such, the claims are fully and adequately enabled. It would require only routine experimentation to determine if *myc* overexpression is suitable for immortalizing antibody secreting cells.

For at least the foregoing reasons, Applicant respectfully submits that Claims 1-5, 7, 8, 18-23 and 25-29 fully comply with 35 U.S.C. § 112, first paragraph, enablement,

and therefore respectfully requests withdrawal of the rejection thereof under 35 U.S.C. § 112.

Rejection under 35 U.S.C. § 103(a)

In the Office Action, beginning at page 10, Claims 1-5, 7, 8, 18-21, 23, and 25-27 were rejected under 35 U.S.C. § 103(a), as reciting subject matters that allegedly are obvious, and therefore allegedly unpatentable, over the disclosure of Zaccolo *et al.* (hereinafter "Zaccolo"), in view of the disclosure of Weissinger *et al.* (hereinafter "Weissinger"), Yu *et al.* (hereinafter "Yu"), and Felsher *et al.* (hereinafter "Felsher"). Applicant respectfully requests reconsideration of this rejection.

Zaccolo is cited for reviewing the state of the art ***in 1993*** with respect to methods of producing antibodies using immortalized cell lines with a focus on improving methodologies for producing immortalized cell lines, humanizing antibodies, and obviating the *in vivo* immunization steps. It is noted that Zaccolo describes the production of immortalized antibody-secreting cells by fusion of immune spleen lymphocytes with a suitable non-secreting myeloma partner, or by immortalizing cells by EB virus infection, and notes the need to improve the immortalization process.

As discussed at the beginning of the present application in paragraphs [0005] to [0017], as of the priority date of the present application, the fusion efficiency was accepted as being relatively inefficient and the majority of efforts to improve the method of immortalization, which were practiced over a considerable period of time, focused on improving the fusion step.

In contrast, the present inventor has devised a completely new strategy that can be used for making immortalised antibody-secreting cells. In the method of the present invention, the animals which are utilized are transgenic and their antibody producing cells have the capacity to be induced into an immortalized state simply by exposing them to a stimulus. Thus, the relatively inefficient step of fusing the antibody-producing cells to myeloma cells, as described in Zaccolo, can be avoided. This has the significant advantage of generating a greater variety of immortalised antibody-secreting cells, and, as a result, a better chance of obtaining clones producing antibodies with industrial utility.

The glaring deficiencies of Zaccolo, in that there is no mention or suggestion of using transgenic animals, are asserted to be obviated by the disclosures of Weissinger, Yu, and Felsher. Weissinger is cited for teaching the use of oncogene expression for direct immortalization of antibody-secreting B lymphocytes. Yu is cited for establishing that it was well known in the art to use transgenic mice to directly immortalize B lymphocytes. Felsher is cited for establishing that the use of an inducible expression system which controls the expression of the *myc* gene for reversible tumorigenesis is known in the art.

It is alleged that the person of ordinary skill in the art would have been motivated to modify the method taught by Zaccolo in view of Weissinger because of the need for improved methods of immortalization. Further, the Examiner alleges that it would have been obvious to the person of ordinary skill to select the teachings of Yu and Felsher as the basis for a modification, which would lead them to the present invention.

In response, the person of ordinary skill in the art would not have selected the documents and teachings by Yu and Felsher to improve the methods of immortalization as taught by Zaccolo and Weissinger. This is because there is nothing in Zaccolo or Weissinger which would lead the person of ordinary skill to Yu and Felsher, which are directed to a completely different field of technology. Furthermore, there is nothing in Yu and Felsher regarding antibody production which would allow the person of ordinary skill to identify these documents ***without a knowledge of the present invention***.

In particular, neither Zaccolo nor Weissinger suggest the use of a transgenic animal wherein the antibody-secreting cells are capable of expression of one or more transgenes, and are in a nonimmortalized state in the absence of a stimulus but are capable of changing to an immortalized state by means of the transgene upon exposure of the cells to the stimulus. Furthermore, the disclosures of both Yu and Felsher are related to the study of cancer and are not concerned with the issue of antibody production.

The study reported by Yu relates to the generation of a non-transgenic mouse model of B-lymphoma to address the specific question as to whether Myc-over-expressing, p53-null B-cell precursors are immediately tumorigenic in syngeneic mice (see page 1923, right hand column, end of first paragraph). In particular, the authors are concerned with further understanding the involvement of *c-myc* in haematopoietic

tumors. Clearly, this has nothing to do with antibody production, nor the achieving an immortalized state by means of a transgene upon exposure of the cells to a stimulus, and therefore, cannot be combined with the teachings of Zaccolo or Weissinger.

Turning to Felsher, this document is also concerned with oncology and the question of whether targeted repair of mutant protooncogenes or the inactivation of their gene products may be a specific and effective therapy for human neoplasia (see abstract). To investigate this issue, the authors generate transgenic mice that conditionally express the *myc* protooncogene in hematopoietic cells. The authors demonstrate that sustained expression of the *myc* transgene culminated in the formation of malignant T cell lymphomas and acute myeloid leukemias, while the subsequent inactivation of the transgene causes regression of the established tumours. Neither Yu nor Felsher discusses or suggests antibody production.

Accordingly, the combination of the teachings of Zaccolo, Weissinger, Yu and Felsher would not have been made by the person skilled in the art at the priority date of the invention. Such a combination can only be made in hindsight, with the benefit of the knowledge of the present invention. Clearly, the disparate teachings of these four references do not combine to render the claimed invention obvious, in that the person of ordinary skill in the art would have no reason, suggestion, or logical rationale to combine their disparate teachings. Yu and Felsher deal exclusively with oncogensis and the study of cancer, whereas the Zaccolo and Weissinger merely teach old technology in the study of immortalization of antibody-secreting cells. For these reasons, the combination of references as cited cannot render the claimed invention obvious.

For at least the foregoing reasons, Applicant respectfully submits that the subject matters of Claims 1-5, 7, 8, 18-21, 23, and 25-27, each taken as a whole, would not have been obvious to one of ordinary skill in the art at the time of Applicant's invention, are therefore not unpatentable under 35 U.S.C. § 103(a), and therefore respectfully requests withdrawal of the rejection thereof under 35 U.S.C. § 103(a).

In the Office Action, beginning at page 13, Claim 22 was rejected under 35 U.S.C. § 103(a), as reciting subject matters that allegedly are obvious, and therefore allegedly unpatentable, over the disclosure of Zaccolo in view of the disclosure of

Weissinger, Yu, and Felsher, as applied to the claims as above, and further in view of Irsch *et al.* (hereinafter "Irsch"). Applicant respectfully requests reconsideration of this rejection.

The teachings of the first 4 references are explained and rebutted above. Irsch is cited for teaching that the technique of selecting desirable immortalized cells via fluorescence activated cell sorting is known. However, it is explained above that the combination of the first 4 references is clearly deficient in rendering obvious the claimed invention, and the teachings of Irsch does not make up for these clear deficiencies. Thus, assuming *arguendo* that a person of ordinary skill the art would find a reason, related to the subject matters of the various prior art documents, to combine their disclosures in the manner alleged in the Office Action to be obvious, the resulting hypothetical construct would still not include each and every feature recited in combination of the pending claims, at least because Zaccolo, Weissinger, Yu, and Felsher fail to describe the claimed method of producing immortalized cells, and Irsch fails to disclose, describe, or fairly suggest curing this deficiency with respect to the combinations of the pending claims. Therefore, this combination of references cannot render obvious the claimed invention of claim 22.

For at least the foregoing reasons, Applicant respectfully submits that the subject matter of Claim 22 would not have been obvious to one of ordinary skill in the art at the time of Applicant's invention, are therefore not unpatentable under 35 U.S.C. § 103(a), and therefore respectfully requests withdrawal of the rejection thereof under 35 U.S.C. § 103(a).

In the Office Action, beginning at page 13, Claim 25 was rejected under 35 U.S.C. § 103(a), as reciting subject matters that allegedly are obvious, and therefore allegedly unpatentable, over the disclosure of Zaccolo in view of the disclosure of Weissinger, Yu, Felsher, and further in view of No *et al.* (hereinafter "No"). Applicant respectfully requests reconsideration of this rejection.

The teachings of the first 4 references are explained and rebutted above. No is cited for teaching that the technique of controlling gene expression in mammalian cells and transgenic mice is known. However, it is explained above that the combination of

the first 4 references is clearly deficient in rendering obvious the claimed invention, and the teachings of No does not make up for these clear deficiencies. Thus, assuming *arguendo* that a person of ordinary skill the art would find a reason, related to the subject matters of the various prior art documents, to combine their disclosures in the manner alleged in the Office Action to be obvious, the resulting hypothetical construct would still not include each and every feature recited in combination of the pending claims, at least because Zaccolo, Weissinger, Yu, and Felsher fail to describe the claimed method of producing immortalized cells, and No fails to disclose, describe, or fairly suggest curing this deficiency with respect to the combinations of the pending claims. Therefore, this combination of references cannot render obvious the claimed invention of claim 25.

For at least the foregoing reasons, Applicant respectfully submits that the subject matter of Claim 25 would not have been obvious to one of ordinary skill in the art at the time of Applicant's invention, are therefore not unpatentable under 35 U.S.C. § 103(a), and therefore respectfully requests withdrawal of the rejection thereof under 35 U.S.C. § 103(a).

In the Office Action, beginning at page 14, Claims 28 were rejected under 35 U.S.C. § 103(a), as reciting subject matters that allegedly are obvious, and therefore allegedly unpatentable, over the disclosure of Zaccolo in view of the disclosure of Weissinger, Yu, and Felsher, and further in view of Yokoyama. Applicant respectfully requests reconsideration of this rejection.

The teachings of the first 4 references are explained and rebutted above. Yokoyama is cited for teaching that the technique of preserving cells and hybridoma is known. However, it is explained above that the combination of the first 4 references is clearly deficient in rendering obvious the claimed invention, and the teachings of Yokoyama does not make up for the clear deficiencies. Thus, assuming *arguendo* that a person of ordinary skill the art would find a reason, related to the subject matters of the various prior art documents, to combine their disclosures in the manner alleged in the Office Action to be obvious, the resulting hypothetical construct would still not include each and every feature recited in combination of the pending claims, at least because Zaccolo, Weissinger, Yu, and Felsher fail to describe the claimed method of producing

immortalized cells, and Yokoyama fails to disclose, describe, or fairly suggest curing this deficiency with respect to the combinations of the pending claims. Therefore, this combination of references cannot render obvious the claimed invention of claim 28.

For at least the foregoing reasons, Applicant respectfully submits that the subject matter of Claim 28 would not have been obvious to one of ordinary skill in the art at the time of Applicant's invention, are therefore not unpatentable under 35 U.S.C. § 103(a), and therefore respectfully requests withdrawal of the rejection thereof under 35 U.S.C. § 103(a).

Conclusion

For at least the foregoing reasons, Applicant respectfully submits that the present patent application is in condition for allowance. An early indication of the allowability of the present patent application is therefore respectfully solicited.

If Examiner Li believes that a telephone conference with the undersigned would expedite passage of the present patent application to issue, she is invited to call on the number below.

It is not believed that extensions of time are required, beyond those that may otherwise be provided for in accompanying documents. However, if additional extensions of time are necessary to prevent abandonment of this application, then such extensions of time are hereby petitioned under 37 C.F.R. § 1.136(a), and the Commissioner is hereby authorized to charge fees necessitated by this paper, and to credit all refunds and overpayments, to our Deposit Account 50-2821.

Respectfully submitted,

By: /Shelly Guest Cermak/
Shelly Guest Cermak
Registration No. 39,571

U.S. P.T.O. Customer No. 38108
Cermak Kenealy Vaidya & Nakajima LLP
515 E. Braddock Road
Alexandria, VA 22314
703.778.6608

Date: September 11, 2009